IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 3728
UMAÑA *et al.*	Art Unit: 1633
Appl. No.: 10/761,435	Examiner: BURKHART, Michael D.
Filed: January 22, 2004	Atty. Docket: 1975.0180003/TJS/M-N/MSS
For: **Fusion Constructs and Use of Same to Produce Antibodies with Increased Fc Receptor Binding Affinity and Effector Function**	

Declaration of Pablo Umaña Under 37 C.F.R. § 1.132

Mail Stop Amendment

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Pablo Umaña, declare and state that:

1. I received my Ph.D. in 1998 from California Institute of Technology, Pasadena, CA A copy of my *curriculum vitae* is attached hereto as Exhibit 1.

2. I am currently employed at Roche Glycart AG., where I hold the position of Chief Scientific Officer. I have particular expertise in polypeptide glycoengineering, including glycoengineering of antibodies for enhanced effector function. I have conducted cutting-edge research in this field and have published extensively. I am qualified to speak to the results reported in U.S. Publ. No. 2004/0241817, and I am the lead inventor in U.S. Appl. No. 10/761,435, as well as PCT Publ. No. WO 1999/054342

3. I have read and understand the above-identified application, the pending claims, as well as the Office Actions of January 21, 2010, and January 25, 2011.

4. I understand that pending claims 30-34, 65, 68, 74, 82-95, 186, 190, and 206-212 are directed to methods for producing fusion glycosyltransferases and polypeptides glycoengineered by the same and methods for modifying the glycosylation profile of polypeptides using glycosyltransferases.

5. It is also of my understanding that the pending claims have been rejected in the Office Action of January 25, 2011 as allegedly being obvious over Umaña *et al.* (WO 99/54342), Grabenhorst *et al., Journal of Biological Chemistry* 274:36107-36116 (1999) and Shields *et al., Journal of Biological Chemistry* 277:26733-26740 (2002) in view of Russel *et al.* (WO 01/29242 A2) and Rabouille *et al., Journal of Cell Science* 108:1617-1627 (1995). I understand that the earliest effective filing date of this application is January 22, 2004 and that this application claims the benefit of priority to U.S. Prov. Appl. Nos. 60/441,207, filed 01/22/2003; 60/491,254, filed 07/31/2003; and 60/495,142, filed 08/15/2003.

6. It is also my understanding, based on my review of the Office Actions of January 21, 2010, and January 25, 2011, that the Examiner believes that a skilled scientist would have been motivated by the cited references with a reasonable expectation of success to generate the claimed fusion glycosyltransferases in order to modify the glycosylation profile of an antibody for the purpose of enhancing Fc-receptor binding and effector functions. (Office Action of January 21, 2010, at pages 2-4 and Office Action of January 25, 2011, at pages 4-5)

7. I disagree. Upon reviewing the documents relied on by the Examiner, it is my opinion that a skilled scientist would not have had a reasonable expectation of

successfully enhancing antibody Fc-receptor binding and effector function when the claimed fusion glycosyltransferases are expressed for the following reasons: (i) the cited documents do not teach the use of a fusion glycosyltransferase comprising GnT III activity and the Golgi localization domain of a Golgi resident polypeptide other than GnT III; (ii) the cited documents do not teach the glycoengineering strategy embodied in the pending claims, and Umaña *et al.* and Shields *et al.* teach away from the pending claims; and (iii) a skilled scientist could not have predicted, based on the disclosure of the cited references, the unexpected superior results as discussed in further detail later in this declaration. For these reasons, which are discussed individually in further detail below, one of ordinary skill in the art would not have had a reasonable expectation of success in carrying out the glycoengineering strategy detailed in the present application based on the disclosure of the cited references.

8. It is my opinion that the present specification demonstrates unexpected, beneficial results that could have been predicted by a skilled scientist based upon the disclosure of the cited references. For example, Figures 2, 3 and 4 of the specification demonstrate that cells expressing the fusion glycosyltransferase with GnT III activity and a Man II localization domain (Man II-GnT III) more efficiently produced antibodies with higher ADCC, as compared to those antibodies produced within cells expressing fusion glycosyltransferases with either GnT III activity and a GnT I localization domain (GnT I-GnT III) or GnT III activity and a WT localization domain (WT-GnT III). *See* specification at page 98, paragraph 255. This result is unexpected based on the co-distribution of ManII and GnTI in the Golgi. *See* specification at page 98, paragraph

255. Given the co-distribution of ManII and GnTI within the Golgi sub-compartments, a skilled scientist would predict that similar glycosylation profiles of target polypeptides would result from two fusion glycosyltransferases having a common GnT III glycosyltransferase domain and either a Man II or GnT I localization domain. These unexpected and beneficial results could not have been predicted by one of ordinary skill in the art based upon the teachings of Grabenhorst *et al.* concerning the mapping of Golgi polypeptides or by the teachings of the other cited references.

9. It is my understanding, based on my review of the Office Action dated January 25, 2011, for example at page 5, that the Examiner has indicated that Umaña *et al.* teach the modification of the glycosylation profile of antibodies for increased ADCC via redistribution of the desired glycosyltransferases and that the Applicants' claims are a simple and obvious alternative. The Examiner states the following:

> Umana et al suggest one way of doing so is to modify the distribution of GalT such that it is found after GnTIII in the glycosylation pathway. Moving GnTIII to a point before GalT in said pathway is a simple and obvious alternative, for reasons of record, to moving GalT. One of skill in the art would expect after such a redistribution not only a change in the glycosylation profile, but a profile that according to Umana et al would increase ADCC.

See Office Action dated January 25, 2011 at page 5.

I disagree with the Examiner's argument for a number of reasons. (i) The strategy proposed by Umaña *et al.* is hypothetical and has the intended purpose of reducing non-

galactosylated oligosaccharides **if** galactosylated oligosaccharides are found to have increased ADCC. The claims of the pending application, however, do not distinguish between increasing galactosylated over non-galactosylated oligosaccharides. Therefore the proposed strategy of Umaña *et al.* does not relate to the claimed invention. (ii) Umaña *et al.* teach away from the Applicants' glycoengineering strategy in the paragraph preceding that referenced by the Examiner. *See* WO 99/54342 at page 39, lines 4-19. Specifically, Umaña *et al.* teach multiple strategies involving the manipulation of glycosyltransferase co-substrates to alter polypeptide glycosylation. In one strategy, for example, Umaña *et al.* teach genetically altering sugar nucleotide transport into the Golgi. (iii) The fusion glycosyltransferase strategy proposed by Umaña *et al.* would relocalize Gal T from the trans-Golgi cisterna to the trans-Golgi network. The glycoengineering strategy of the current application, however, involves the relocalization of GnT III activity from the trans-Golgi cisterna towards the cis-Golgi cisterna. Therefore, the glycoengineering strategy claimed by the Applicants differs from the strategy proposed by Umaña *et al.* in that different polypeptides with differing enzymatic activities are being relocalized and the direction of relocalization in the Applicants' claimed glycoengineering strategy (directionally from trans to cis) is opposite to that proposed by Umaña *et al.*

For the reasons described in points (ii) and (iii), Umaña *et al.* teach away from the Applicants' glycoengineering strategy. Therefore, it cannot be argued that the pending claims are a simple variation of the approach proposed by Umaña *et al.* to achieve the same outcome, particularly in light of the differing end-goals as explained in

point (i). Furthermore, the differences in enzymatic activity and direction of localization between the fusion glycosyltransferases disclosed by the Applicants and the one proposed by Umaña *et al.* would result in different glycosylation profiles of the target polypeptides.

10. It is my understanding, based on my review of the Office Actions dated January 21, 2010, and January 25, 2011, that the Examiner believes that a skilled scientist would be able to combine the cited references to arrive at the claimed invention. However, Umaña *et al.*, Grabenhorst *et al.*, and Shields *et al.* do not individually or in combination disclose the claimed method of enhancing antibody effector function and Fc-receptor binding via the activities of fusion glycosyltransferases comprising a GnT III glycosyltransferase domain with a heterologous Golgi localization domain. Nor do the cited references create a logical "road map" towards the design of the glycoengineering strategy disclosed in the present specification. As indicated above, Umaña *et al.* propose in a hypothetical context a fusion glycosyltransferase that would yield a different glycosylation profile compared to those obtained using the glycoengineering strategy claimed herein. While Grabenhorst *et al.* do relocalize the glycosyltransferase FT-6, which was used as a reporter in the assays, by constructing fusion peptides with various Golgi localization domains, the intent of the study was to map the localization of glycosyltransferases within the Golgi/trans-Golgi network. The scientific work described in Grabenhorst *et al.* does not involve relocalization of GnT III activity in their assays and does not predict the effects of GnT III relocalization on glycosylation of <u>any</u> polypeptide. Therefore, the combination of scientific contributions set forth in these two

cited references would not guide a skilled scientist towards the claimed glycoengineering strategy.

Shields *et al.* only focuses on a fucosylation-deficient CHO cell line variant that produces antibodies with enhanced Fc-receptor affinity. This reference does not indicate the biochemical origin of the cell line's inability to add fucose to IgG1 and does not enable a scientist to predict the effects of GnT III relocalization on the glycosylation profiles of polypeptides. The only recommendation concerning glycoengineering of antibodies made by Shields *et al.* is the treatment of fucosylated IgG with fucosidases. Therefore, Shields *et al.* teach away from the pending claims.

Even if the cited references gave a reasonable expectation of success, which they do not, only substantial and labor-intensive experimentation would reveal the actual glycosylation profile of a target polypeptide yielded by expression of a specific fusion glycosyltransferase and whether or not a given glycosylation profile is associated with enhanced function of the target polypeptide. Furthermore, only experimentation would determine that a specific fusion glycosyltransferase displays unpredictable and beneficial characteristics, as was the case with both the results disclosed in the post-filing publication Ferrara *et al.*, *Biotech. Bioeng.* *93*:851-861 (2006) and the previously discussed example of the Man II-GnT III fusion glycosyltransferase.

11. There are many alternative strategies that a skilled scientist could implement in their attempt to enhance antibody function by glycoengineering, including, but not limited to, overexpression of single or multiple glycosyltransferases, regulated or "on/off" expression of single or multiple glycosyltransferases, knocking out expression

of glycosyltransferases, targeted mutations of glycosyltransferases, relocalization of the desired glycosyltransferase to the desired Golgi compartment, relocalization of the undesired glycosyltransferase away from the desired Golgi compartment, treatment of antibodies with fucosidases, and targeting of fucosidases to the desired Golgi compartment. As mentioned above, many of these alternative strategies are disclosed by the cited references. The cited references, however, do not provide evidence that the Applicants' glycoengineering strategy would successfully produce antibodies with increased ADCC, nor do the cited references provide evidence suggesting that the Applicants' glycoengineering strategy would be superior to these alternative glycoengineering strategies. Therefore, it cannot be concluded that the cited references in combination provide a logical road map to the Applicants' claimed method of generating antibodies with increased ADCC.

12. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

13. I have read, I am familiar with, and I understand, the provisions of 37 C.F.R.§§ 11.18(b) and (c) relating to the effect of signature and certificate for correspondence filed in the U.S. Patent and Trademark Office.

Date: July 22nd, 2011

Pablo Umaña, Ph.D.

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